Relation between the kinetics of thallium-201 in myocardial scintigraphy and myocardial metabolism in patients with acute myocardial infarction

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Abstract

Objective—To investigate the relations between myocardial metabolism and the kinetics of thallium-201 in myocardial scintigraphy.

Methods—46 patients within six weeks after the onset of acute myocardial infarction underwent resting myocardial dual isotope, single acquisition, single photon emission computed tomography (SPECT) using radiiodinated 15-iiodophenyl 3-methyl pentadecanoic acid (BMIPP) and thallium-201, exercise thallium-201 SPECT, and positron emission tomography (PET) using nitrogen-13 ammonia (\(\text{NH}_3\)) and \([\text{F}^{18}\text{]fluorodeoxyglucose (FDG)}\) under fasting conditions. The left ventricle was divided into nine segments, and the severity of defects was assessed visually.

Results—In the resting SPECT, less BMIPP uptake than thallium-201 uptake was observed in all of 40 segments with reverse redistribution of thallium-201, and in 21 of 88 segments with a fixed defect of thallium-201 (p < 0.0001); and more FDG uptake than NH\(_3\) uptake (NH\(_3\)--FDG mismatch) was observed in 35 of 40 segments with reverse redistribution and in 38 of 88 segments with fixed defect (p < 0.0001). Less BMIPP uptake in the resting SPECT was observed in 49 of 54 segments with slow stress redistribution in exercise SPECT, and in nine of 17 segments with rapid stress redistribution (p < 0.0005); NH\(_3\)--FDG mismatch was observed in 42 of 54 segments with slow stress redistribution and in five of 17 segments with rapid stress redistribution (p < 0.0005).

Conclusions—Thallium-201 myocardial scintigraphy provides information about not only myocardial perfusion and viability but also about myocardial metabolism in patients with acute myocardial infarction.

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Keywords: thallium-201 SPECT; BMIPP SPECT; FDG PET; myocardial infarction; redistribution

In thallium-201 myocardial scintigraphy, perfusion defects in images obtained immediately after exercise (initial image) may be no longer evident in the images obtained several hours after exercise (delayed image). This phenomenon is referred to as redistribution, and is thought to indicate the presence of myocardial ischaemia.

Reverse redistribution refers to perfusion defects that appear, or become more evident, in the delayed images obtained in resting or stress thallium-201 myocardial scans, and is very common in patients with acute myocardial infarction treated with thrombolysis. Although the significance and the mechanism of this phenomenon remain controversial, we have reported that reverse redistribution on resting myocardial scintigraphy in patients with acute myocardial infarction is observed in viable myocardium with severe contraction abnormality, and is closely related to the slow stress redistribution observed in four hour delayed images in exercise scintigraphy.

In many regions of the viable myocardium, perfusion defects that are detected on the initial images persist, and appear to be irreversible, on delayed images obtained three to four hours after exercise. Some persistent defects appear to have improved in the delayed images obtained eight to 72 hours after thallium-201 injection, in images obtained after reinjection of additional thallium-201, or when a resting study is repeated with an additional injection of thallium-201. Thus it is widely accepted that perfusion defects observed in the delayed image obtained three to four hours after exercise underestimate the viability of myocardium in the infarct region, and that the redistribution in the delayed image obtained three to four hours after exercise is insufficient.

Myocardial metabolic imaging with the use of fatty acid analogues and glucose analogues has recently become available. Radioiodinated 15-iiodophenyl 3-methyl pentadecanoic acid (BMIPP) is used clinically as a probe for studying the myocardial metabolism of fatty acids. Positron emission tomography (PET) allows assessment of regional myocardial perfusion and metabolism in vivo. Hypoperfused myocardium with an increased uptake of [F\(^{18}\)]fluorodeoxyglucose (FDG) as an indicator of exogenous glucose utilisation is considered to be an ischaemic but viable myocardium with potential for improvement in regional function after the restoration of blood flow.

Although Matsunari \textit{et al} have reported that fatty acid uptake is impaired in the area of fill-in after reinjection on exercise thallium-201 scintigraphy, the relation between myocardial metabolism and the kinetics of thallium-201...
remains to be clarified. Our aim in this study was to measure the uptake of fatty acids and glucose in the myocardium, demonstrating reverse redistribution in resting thallium-201 myocardial scintigraphy or slow stress redistribution on the four hour delayed image from exercise thallium-201 scintigraphy. Uptake was measured using BMIPP single photon emission computed tomography (SPECT) and FDG PET.

**Methods**

**PATIENT POPULATION**

Forty six patients with acute myocardial infarction (39 men and seven women; mean (SD) age 60 (10) years, range 33 to 74 years) who were admitted to the coronary care unit of Osaka City University Medical School Hospital between October 1993 and June 1996 and underwent resting myocardial dual isotope, single acquisition SPECT using BMIPP and thallium-201, exercise thallium-201 SPECT and PET using FDG and nitrogen-13 ammonia (NH₃) in the subacute phase (within six weeks after the onset of myocardial infarction) were selected for the present study retrospectively from our patient database. Acute myocardial infarction was defined by the presence of typical chest pain, depression or elevation of the ST segment on standard 12 lead electrocardiogram, and a rise in serum creatine kinase or the creatine kinase MB isoenzyme to more than three times the upper limit of normal. Patients with a history of previous myocardial infarction or of coronary artery bypass grafting were excluded from the study. Twenty six patients had anterior infarction and 20 had inferior infarction.

The mean (SD) intervals between myocardial infarction and resting SPECT, exercise SPECT, and PET were 16 (9), 24 (8), and 21 (11) days, respectively. Three scintigraphic studies for each patient were performed within three weeks.

**RADIOPHARMACEUTICALS**

BMIPP, an iodine-123 labelled β methyl branched fatty acid analogue, was prepared and supplied by Nihon Medi-Physics Co (Hyogo, Japan). Thallium-201 was obtained from commercial laboratories.

A small cyclotron (NKK Corporation, Kanagawa, Japan) was used for production of nitrogen-13 and fluorine-18. NH₃ was produced by the method reported by Mulholland et al. FDG was synthesised by the method reported by Hamacher et al.

**RESTING BMIPP AND THALLIUM-201 DUAL ISOTOPE SPECT**

After overnight fasting, each patient received an intravenous injection of BMIPP (111 MBq) and thallium-201 (111 MBq) at rest. Initial images were obtained 20 minutes after the injection, and delayed images were obtained four hours later. SPECT was performed using a single head gamma scintillation camera equipped with a low energy, all purpose parallel hole collimator. Thirty two equidistant projections were acquired (30 s/projection) over 180° from the right anterior oblique to the left posterior oblique. The images from the two energy windows (159 keV ± 7.5% for iodine-123 and 70 keV ± 10% for thallium-201) were collected in separate 64 × 64 matrices and then reconstructed using the Butterworth filter and Shepp and Rogan filter along the short axis, the horizontal long axis, and the vertical long axis of the heart. Images were normalised to the maximum count in each image set, and displayed as a colour scale image by a computer system (Scintipac-7000, Shimadzu Corporation, Kyoto, Japan). No downscatter correction was performed.

**EXERCISE THALLIUM-201 SPECT**

Each patient performed symptom limited exercise on a bicycle ergometer in the sitting position. Twelve lead electrocardiograms and blood pressure measurements were obtained at baseline and at every minute of exercise. The initial workload was 25 or 50 watts and was increased by 25 watts every two minutes until the end point of the exercise was reached. The end point included excessive fatigue, dyspnoea, dizziness, moderate to severe angina, hypotension, diagnostic ST depression (> 1.5 mm horizontal or downsloping, or > 2.0 mm upsloping), or significant arrhythmia. At peak exercise, a dose of 111 MBq thallium-201 was injected intravenously and the patient was encouraged to exercise for an additional minute. Initial images were obtained immediately after the termination of exercise and delayed images were obtained four hours later. SPECT was performed as in the resting study.

**PET IMAGING**

PET imaging was performed with a Shimadzu SET 1400 W-10 PET scanner (Headtome IV, Shimadzu Corporation). This can obtain seven slices simultaneously with a 13 mm interval, slice thickness of 11 mm FWHM, and spatial resolution of 4.5 mm FWHM. The axial, 6.5 mm interval, Z motion of the scanner every minute provided a total of 14 contiguous transverse slices of the myocardium. A 10 minute transmission scan was performed using a rotating germanium-68 rod source. The acquired data were used to correct emission images for body attenuation. On completion of the attenuation scan, the patient remained in the supine position on the table and was injected intravenously with 259 to 740 MBq of NH₃. After a three minute delay to allow pulmonary background activity to clear, myocardial perfusion imaging was performed for 10 minutes.

After at least five hours of fasting and two to three hours after the perfusion scan, the patient received an intravenous injection of 148 to 407 MBq of FDG. Sixty minutes were allowed for cardiac uptake of FDG. Imaging of glucose utilisation was then obtained for 10 minutes.

Images were collected in 256 × 256 matrices and then reconstructed using the Butterworth filter and the Ramp filter along the short axis, the horizontal long axis, and the vertical long axis of the heart by a computer system (Dr...
**FLUORODEOXYGLUCOSE; NH₃, NITROGEN-13 AMMONIA**

BMIPP, radio-iodinated 15-iodophenyl 3-methyl pentadecaenoic acid; FDG, [F18]fluorodeoxyglucose; NH₃, nitrogen-13 ammonia.

**BMIPP > Tl implies a BMIPP defect score larger than the corresponding thallium-201 defect score.**

**Redistribution Patterns of Resting Thallium-201 SPECT**

Relative to the defect score of the initial image, a decrease in defect score of the delayed image was defined as rest redistribution and an increase was defined as reverse redistribution. Fixed defect was defined as the defect of the delayed image equal to that of the initial image for scores not equal to zero.

**COMPARISON OF RESTING BMIPP AND THALLIUM-201 IMAGES**

Comparison of defects on resting BMIPP and thallium-201 images was performed for each initial image. A segment was determined to be BMIPP > T1 when the defect score of the BMIPP image was larger than that of the thallium-201 image, which was considered to represent decreased fatty acid uptake compared with myocardial perfusion. Similarly, a segment was determined to be BMIPP = T1 when the defect scores of the BMIPP image and the thallium-201 image were equal, which was considered to represent matched fatty acid uptake and myocardial perfusion.

**Comparison of resting BMIPP and thallium-201 images**

**Table 1 Thallium-201 redistribution pattern and defect score of the initial image on resting SPECT (number of segments)**

<table>
<thead>
<tr>
<th>Defect score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed defect</td>
<td>0</td>
<td>10</td>
<td>23</td>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>Reverse redistribution</td>
<td>5</td>
<td>14</td>
<td>10</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Redistribution</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

| p Value | < 0.0001 |

**Table 2 Relation between redistribution pattern of resting thallium-201 SPECT and myocardial metabolism (number of segments)**

<table>
<thead>
<tr>
<th>Resting BMIPP-thallium-201</th>
<th>NH₃-FDG-PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMIPP = T1</td>
<td>Match</td>
</tr>
<tr>
<td>BMIPP &gt; T1</td>
<td>Mismatch</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fixed defect</th>
<th>67</th>
<th>21</th>
<th>50</th>
<th>38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reverse redistribution</td>
<td>0</td>
<td>40</td>
<td>5</td>
<td>35</td>
</tr>
<tr>
<td>Redistribution</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

| p Value | < 0.0001 | < 0.0001 |

BMIPP, radio-iodinated 15-iodophenyl 3-methyl pentadecaenoic acid; FDG, [F18]fluorodeoxyglucose; NH₃, nitrogen-13 ammonia.

BMIPP > T1 implies a BMIPP defect score larger than the corresponding thallium-201 defect score.
BMIPP, radio-iodinated 15-iodophenyl 3-methyl pentadecaenoic acid; FDG, [F18]fluorodeoxyglucose; NH$_3$, nitrogen-13 ammonia.

$\text{BMIPP > T1}$ implies a BMIPP defect score larger than the corresponding thallium-201 defect score.

FDG uptake was definitely higher than both NH$_3$ uptake of the segment and FDG uptake of non-infarcted segments (this was considered to represent increased glucose uptake compared with myocardial perfusion), and was defined as matched when FDG uptake was less than or similar to NH$_3$ uptake of the segment (this was considered to represent matched glucose uptake compared with myocardial perfusion$^5$).

**Table 3** Relation between the findings of exercise thallium-201 SPECT and myocardial metabolism (number of segments)

<table>
<thead>
<tr>
<th>Exercise induced ischaemia</th>
<th>BMIPP = T1</th>
<th>BMIPP &gt; T1</th>
<th>Match</th>
<th>Mismatch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>65</td>
<td>8</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>Positive</td>
<td>8</td>
<td>9</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Rapid stress redistribution</td>
<td>5</td>
<td>49</td>
<td>12</td>
<td>42</td>
</tr>
<tr>
<td>Slow stress redistribution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p Value</td>
<td>&lt; 0.0005</td>
<td>&lt; 0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4** Relation between the findings of resting and exercise thallium-201 SPECT (number of segments)

<table>
<thead>
<tr>
<th>Exercise thallium-201 SPECT</th>
<th>Fixed defect</th>
<th>Reverse redistribution</th>
<th>Redistribution</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise induced ischaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>61</td>
<td>2</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid stress redistribution</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Slow stress redistribution</td>
<td>4</td>
<td>36</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt; 0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RESULTS**

**Reverse Redistribution of Thallium-201 on Resting SPECT and Myocardial Metabolism**

Resting thallium-201 SPECT showed 88 segments with a fixed defect, 40 with reverse redistribution, and eight with redistribution in infarct related territories. The distribution of defect scores of the initial images on resting thallium-201 SPECT are shown in table 1. Defects with reverse redistribution contained more defects with small defect scores than those with fixed defects. The incidence of BMIPP $>$ T1 and NH$_3$–FDG mismatch was significantly higher in segments with reverse redistribution than in segments with a fixed defect (table 2). In the 57 segments with a defect score of 4 from the delayed images in resting SPECT, 10 of 12 segments (83%) with reverse redistribution showed NH$_3$–FDG mismatch, while only 16 of 45 segments (36%) with a fixed defect showed NH$_3$–FDG mismatch (p < 0.01).

**Slow Stress Redistribution of Thallium-201 on Delayed Image from Exercise SPECT and Myocardial Metabolism**

In 144 segments of infarct related territories, defect scores of initial image of exercise thallium-201 SPECT were equal to or greater than 1. Of these segments, 73 were negative for exercise induced ischaemia. Of the 71 segments with exercise induced ischaemia, 17 showed rapid stress redistribution on delayed image from exercise SPECT and 54 showed slow stress redistribution. The incidence of BMIPP $>$ T1 and NH$_3$–FDG mismatch was significantly higher in segments with slow stress redistribution than in segments with rapid stress redistribution or in segments without exercise induced ischaemia (table 3).

**Relation between Exercise and Resting Thallium-201 SPECT**

In 73 segments without exercise induced ischaemia, only two (3%) showed reverse redistribution on resting thallium-201 SPECT. In 17 segments with exercise induced ischaemia and rapid stress redistribution, only two (12%) showed reverse redistribution on resting thallium-201 SPECT, but in 54 segments with exercise induced ischaemia and slow stress redistribution, 36 (67%) showed reverse redistribution (table 4, fig 2).

**Severity of Stenosis of Infarct Related Artery and Kinetics of Thallium-201**

Segments with reverse redistribution were supplied by fewer stenotic arteries than segments with fixed defect on resting thallium-
201 SPECT (table 5). Four of eight segments with rest redistribution had collateral circulation. Segments with exercise induced ischaemia and slow stress redistribution were supplied by arteries that were less stenotic than arteries supplying segments without exercise induced ischaemia, or segments with exercise induced ischaemia and rapid stress redistribution (table 6).

**Discussion**

Our study shows that the incidence of discordant uptake of BMIPP (that is, uptake less than that of thallium-201) and discordant uptake of FDG (that is, more than that of NH₃) was significantly higher in myocardial segments with reverse redistribution of thallium-201 on resting SPECT or with slow stress redistribution of thallium-201 on delayed images from exercise SPECT. We are not aware of any previous reports investigating both fatty acid and glucose metabolism in the myocardium that show reverse redistribution of thallium-201 on exercise-redistribution SPECT; they reported that in 16 patients assessed by PET, all regions with reverse redistribution had viable myocardium. The finding of reverse redistribution on exercise thallium-201 SPECT is consistent with the finding of reverse redistribution on resting thallium-201 SPECT in our study. Matsunari et al have investigated the relation between myocardial fatty acid metabolism and new fill-in after thallium-201 reinjection in patients with chronic coronary artery disease and persistent defects on standard exercise redistribution thallium-201 imaging. BMIPP uptake was found to be less than thallium-201 uptake on reinjection imaging in 82% of myocardial segments with new fill-in after reinjection, but only 19% of segments with no fill-in discordantly decreased BMIPP uptake. Thallium-201 reinjection imaging was used to assess resting myocardial perfusion and for comparison with resting BMIPP imaging, but the reinjection image is not strictly comparable with the resting perfusion image. In contrast, we used resting BMIPP and thallium-201 dual isotope SPECT in our study, and this allowed precise comparison of fatty acid uptake and resting perfusion.

In patients with chronic coronary artery disease the incidence of NH₃–FDG mismatch has been found to be significantly higher in myocardial segments with new fill-in after thallium-201 reinjection than in segments with redistribution on delayed images. These findings are consistent with the results of the present study in segments with slow or rapid
stress redistribution on delayed image from exercise SPECT.

RELATION BETWEEN RESTING REVERSE REDISTRIBUTION AND SLOW STRESS REDISTRIBUTION

The time required to complete thallium-201 redistribution following stress has been reported to be related to the severity of stenosis in the coronary artery supplying the area concerned. However, in the present study segments with exercise induced ischaemia and slow stress redistribution in exercise SPECT were supplied by less stenotic arteries than segments with exercise induced ischaemia and rapid stress redistribution. Also, the segments with reverse redistribution in resting SPECT were supplied by less stenotic arteries than segments with a fixed defect. In acutely infarcted myocardium, conditions other than myocardial regional blood flow (that is, uptake and washout rate of thallium-201 in the myocardium) may play a part in the reverse redistribution during resting scintigraphy and the slow stress redistribution during exercise study.

Weiss et al have reported that all acute myocardial infarcts with reverse redistribution in resting scintigraphy had patent infarct related coronary arteries. However, Hecht et al have reported that 85% of patients with reverse redistribution during stress scintigraphy have a stenosed coronary artery (> 90% stenosis). It has also been reported that reverse redistribution does not correlate closely with the degree of coronary artery disease. These differences among the previous and the present studies are thought to be caused by the differences of patient population, the time of the test, and the definition of reverse redistribution of each report.

The results of our study indicate that in myocardial segments with reverse redistribution on resting SPECT or slow stress redistribution on exercise SPECT, the major energy source changed from fatty acids to glucose, perhaps leading to a decrease in ATP production. Reverse redistribution on resting thallium-201 SPECT was reported in viable myocardium with severe contraction abnormality in patients with acute myocardial infarction. Also, a strong correlation has been observed between the degree of reverse redistribution on resting thallium-201 SPECT and the degree of insufficiency of redistribution on delayed images from exercise thallium-201 SPECT. The correlation between reverse redistribution on resting SPECT and slow stress redistribution on delayed images from exercise SPECT was also observed in the present study. Accordingly, we thought that the phenomena of reverse redistribution in resting SPECT and slow stress redistribution in exercise SPECT might have a common mechanism related to the metabolic abnormality of the myocardium.

STUDY LIMITATIONS

The patient selection in our study was performed retrospectively, and was biased. As a result, most of the patients had single vessel disease. We also assessed the SPECT and PET images visually. To confirm our results, quantitative analysis in a larger patient population should be performed, including many patients with multivessel disease.

We did not investigate the relation between thallium-201 kinetics and the left ventricular wall motion abnormality or its serial changes, which would be necessary to confirm whether decreased BMIPP uptake and increased FDG uptake under fasting conditions indicates potential reversibility of the wall motion abnormalities after revascularisation.

CONCLUSIONS

Our results suggest that thallium-201 kinetics that indicate the presence of reverse redistribution on resting SPECT or slow stress redistribution on exercise SPECT are strongly correlated with abnormality of myocardial metabolism, as indicated by a decrease in fatty acid uptake and an increase in glucose uptake. Our study shows that thallium-201 myocardial scintigraphy provides information not only about myocardial perfusion and viability but also about myocardial metabolism in patients with acute myocardial infarction.

We greatly appreciate the secretarial assistance of Ms Harumi Baba and Ms Ayako Kobayashi. We thank the technologists of Division of Nuclear Medicine for their technical assistance.

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\[ \text{F-labeled fluorodeoxyglucose and N-13 ammonia. Circulation} 1983;67:766–78. \]


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